Journal of Affective Disorders 182 (2015) 121–125

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Predictors of functional outcome after a manic episode

C. Mar Bonnín [a], María Reinares [a], Diego Hidalgo-Mazzei [a], Juan Undurraga [a,b], Maria Mur [c], Cristina Sáez [d], Evaristo Nieto [e], Gustavo H. Vázquez [f], Vicent Balanzá-Martínez [g,h], Rafael Tabarés-Seisdedos [g], Eduard Vieta [a,*]

[a] Bipolar Disorders Unit, Hospital Clínic, University of Barcelona, IDIBAPS, CIBERSAM, Catalonia, Barcelona, Spain
[b] Department of Psychiatry, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile
[c] Psychiatric Service, Santa Maria Hospital, IRB Lleida (Biomedicine Research, Institute), University of Lleida, Catalonia, Lleida, Spain
[d] University Psychiatric Hospital, Institut Pere Mata, CIBERSAM, Reus, Catalonia, Spain
[e] Mental Health Division of Althaia, Xarxa Assistencial Universitària de Manresa, Catalonia, Spain
[f] Department of Neuroscience, Palermo University, Buenos Aires, Argentina
[g] Psychiatric Service, La Fe University and Polytechnic Hospital, Department of Medicine, University of Valencia, CIBERSAM, Valencia, Spain
[h] Department of Medicine, University of Valencia, CIBERSAM, INCLIVA, Valencia, Spain

ARTICLE INFO

Article history:
Received 20 March 2015
Received in revised form
22 April 2015
Accepted 24 April 2015
Available online 2 May 2015

Keywords:
Manic episode
Functional outcome
Predictive variables
Follow-up
Bipolar disorder

ABSTRACT

Background: The identification of functional outcome predictors after acute episodes of bipolar disorders (BD) may allow designing appropriate treatment aiming at restoring psychosocial functioning. Our objective was to identify the best functional outcome predictors at a 6-month follow-up after an index manic episode.

Methods: We conducted a naturalistic trial (MANACOR) focusing on the global burden of BD, with special emphasis on manic episode-associated costs. We observed patients with BD seen in services of four hospitals in Catalonia (Spain).The total sample included 169 patients with chronic DSM-IV-TR BD I suffering from an acute manic episode who were followed-up for 6 months. In this subanalysis we report the results of a stepwise multiple regression conducted by entering in the model those clinical and sociodemographic variables that were identified through preliminary bivariate Pearson correlations and using total scores on the Functioning Assessment Short Test (FAST) at the 6-month follow-up as the dependent variable.

Results: Number of previous depressive episodes (Beta=3.25; t=3.23; p=0.002), presence of psychotic symptoms during the manic index episode (Beta=7.007; t=2.2; p=0.031) and the Body Mass Index (BMI) at baseline (Beta=0.62; t=2.09; p=0.041) were best predictors of functional outcome after a manic episode.

Limitations: The main limitations of this study include the retrospective assessment of the episodes, which can be a source of bias, and the 6-month follow-up might have been too short for assessing the course of a chronic illness.

Conclusions: Psychotic symptoms at index episode, number of past depressive episodes, and BMI predict worse outcome after 6 months follow-up after a manic episode, and may constitute the target of specific treatment strategies.

1. Introduction

Bipolar disorder (BD) is a highly prevalent (Catalá-López et al., 2013; Merikangas et al., 2011) and disabling disease (Huxley and Baldessarini, 2007; Judd et al., 2005; Rosa et al., 2008, 2009). Impairment in functional outcome is commonly observed even when patients are euthymic (Bonnín et al., 2010; Rosa et al., 2010; Tohen et al., 2000) and includes multiple areas of functioning (independent living, interpersonal relationships, occupational and educational achievement, recreational enjoyment and sexual activity) (Goldstein et al., 2009; Kauer-Sant'Anna et al., 2009; Rosa et al., 2009; Rosa et al., 2012). Many factors such as sociodemographic, clinical, pharmacological and neurocognitive variables have been associated with functional impairment (for a review see Sanchez-Moreno et al. (2009)).

Studying the factors associated with functional outcome after an acute episode is relevant because it could help to elucidate potential targets for both pharmacological and psychological treatments (Vieta, 2014). Our group already have performed a 6-month follow-up study using the Functioning Assessment Short Test (FAST) scale as

* Correspondence to: Hospital Clinic Villarroel 170, 08036 Barcelona, Spain.
E-mail address: evieta@clinic.ub.es (E. Vieta).

http://dx.doi.org/10.1016/j.jad.2015.04.043
0165-0327/

the primary outcome in a sample of subsyndromal and syndromal patients with BD (Rosa et al., 2011). Nevertheless, in that study, acute patients were included regardless the polarity of the episode (both manic and depressive) and no multivariate analyses were performed in order to find predictive variables associated with functional outcome. Many studies have evaluated potential predictors of functional recovery after a manic episode, especially after a first manic episode (Conus et al., 2006; Jaeger et al., 2007; Kauer-Sant'Anna et al., 2009; Singh et al., 2000; Smith et al., 2014; Tohen et al., 2000; Torres et al., 2011), but when it comes to patients with multiple episodes the evidence is inconsistent. It is known that patients with first-episode bipolar disorder have better functioning that those with multiple episode at one-year follow-up (Rosa et al., 2012), but determinants of functional outcome in chronic patients still remain unclear. The main objective of the present prospective study was to evaluate the baseline clinical and sociodemographic variables that were significantly associated with functional outcome at 6-month follow-up after an acute manic episode in a sample of multiple episodes bipolar patients.

2. Method

2.1. Study design and participants

This is a subanalysis of a naturalistic trial (MANACOR) which aimed at describing the general burden and costs associated with manic episodes in bipolar patients from four hospitals in Catalonia: Hospital Clínic (Barcelona), Santa Maria Hospital (Lleida), Institut Pere Mata (Reus) and Xarxa Assistencial de Manresa (Manresa). The primary analysis (Hidalgo-Mazzei et al., 2015), combined prospective and retrospective data collection and focused on costs. Clinical data was captured prospectively as a part of the systematic assessment of the Barcelona Bipolar Disorders Program (Vieta, 2013) which was also adopted by the other hospitals involved in the study. Pre-planned subanalyses of the study involved the outcome of BD patients with mixed features (Reinares et al., 2015), pharmacological treatment (Grande et al., 2015), and functional outcome as it is reported in the current study.

In total, the study involved 169 patients with a manic episode, treated clinically and followed-up in four different psychiatric services from Catalonia, Spain. The study protocol was reviewed and approved by the ethical committee of each hospital. Inclusion in this study required meeting: (1) diagnostic criteria for bipolar disorder type I with an index/current manic episode according to DSM-IV-TR and having a Young Mania Rating Scale (YMRS) total score $\geq$ 15 (Colom et al., 2002; Young et al., 1978); (2) to be 18 years or older; (3) the present episode could have been handled in an inpatient or outpatient setting, depending on the patient's clinical severity and psychiatrist's decision. The study started in January 2011 and finished in December 2013.

2.2. Procedure and data collection

Sociodemographic information was extracted from the prospective database. Relevant information about the course of bipolar disorder was specifically reviewed and registered: age and polarity of the first and following episodes, suicide attempts and previous hospitalizations. Date, clinical information, employment-functional status and clinical assessments during the index manic episode were also collected as well as the clinical setting and treatment received.

At baseline and follow-up visits, patients were evaluated through standardized clinical measures, included in the bipolar disorders program protocol of each Hospital involved. The systematic follow-up consisted in periodic appointments (baseline; 1-month; 6-month follow-up) with expert psychiatrists which included a clinical interview and assessment of manic symptoms through the Spanish version of the YMRS and depressive symptoms with the 17-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960; Ramos-Brieva and Cordero, 1986). The Spanish version of the Clinical Global Impressions Scale for Bipolar Disorders (CGI-BP) [CGI-BP-M (Spearing et al., 1997; Vieta et al., 2002)] was routinely used as a reference to assess the patient's global clinical state in addition to the FAST (Rosa et al., 2007) which evaluates global functionality. Functional recovery was defined as a FAST total scores $<$ 12. For further details of the study protocol, see Hidalgo-Mazzei et al. (2015).

2.3. Data analyses

Descriptive analyses of sociodemographic variables including age, gender, marital status and employment status, were conducted. Regarding clinical variables, family psychiatric history along with medical and psychiatric comorbidities, polarity of first episode, lifetime psychotic symptoms and rapid cycling were also analyzed through frequencies analyses. Variables related to history of bipolar disorder such as age of onset, number and type of episodes, and number of suicide attempts and hospitalizations/admissions were described by their means and standard deviations. Analyses involved preliminary Pearson bivariate comparisons of the factors associated with the dependent variable, which was the FAST total score at 6-month follow-up. Bivariate associations with qualitative variables were explored using Mann–Whitney U tests. Finally, all the baseline variables that appeared to be associated with the dependent variable, that showed a trend or have demonstrated to be related to functional outcome in previous literature underwent stepwise multiple regression to provide the beta standardized scores of the variables that best predicted FAST scores at 6-month follow-up.

3. Results

3.1. Sociodemographic and clinical characteristics

Of the total sample of 169 bipolar disorder I acute manic patients, 133 were hospitalized (78.7%) and 36 (21.3%) were treated in the outpatient units.

Mean age was 42.5 (12.7) years and men were slightly more prevalent than women (46.2%).

Table 1 shows the demographic and clinical variables of the sample.

At the 6-month assessment, 17% (n=29) of patients were functionally recovered (that is FAST total score $<$ 12). These patients were younger 38.5 (10.9) when compared to the non-functionally recovered group 43.9 (12.8) (p=0.03). Moreover, they presented lower BMI at baseline (23.9 vs. 27.1; p=0.005), fewer number of total episodes (5.1 vs. 8.2; p=0.02) and shorter illness duration (chronicity) (8.5 vs. 15.4; p $<$ 0.001). Both groups did not differ in terms of age at onset (30 vs. 28.5; p=0.47), presence of psychotic symptoms during the index manic episode (45% vs. 56%; p=0.26), or days of hospitalization (17.8 vs. 20.1; p=0.39).

Regarding mood symptomatology, 96 patients (57% of the initial sample) presented full remission from acute symptoms, operationalized as follows: HAMD $\leq$ 8 and YMRS $\leq$ 6. There were no differences in gender regarding symptomatic recovery.

3.2. FAST change and correlations with FAST total score at follow-up

FAST total score decreased significantly (t=8.64; df=147; p $<$ 0.001) from baseline 38.03 (12.3) to the end of follow-up 25.49 (13.8).

FAST total score at the end of follow-up significantly correlated with the following continuous variables collected at baseline: age

Table 1
Clinical and sociodemographic characteristics at baseline.

	Patients presenting a manic episode ($n=169$)
	***N* (SD)**
Age	42.5 (12.7)
Age at onset	28.3 (9.8)
Number of previous episodes	7.4 (6.5)
Number of previous manic episodes	3.1 (2.7)
Number of previous depressive episodes	2.6 (2.4)
Number of previous mixed episodes	0.5 (1.4)
Chronicity (years of illness)	14.3 (11.3)
Body Masss Index (BMI)	26,5 (6.1)
	***N* (%)**
Gender (female)	78 (46.2)
Psychotic symptoms present episode	96 (56.8)
Rapid cycling	8 (4.7)
Psychiatric comorbidity	41 (24.7)
Marital status	
Single	70 (41.4)
Married/Living as a couple	63 (37.3)
Divorced	30 (17.8)
Widowed	6 (3.6)
Unemployed due to illness	71 (42.5)
Pharmacological treatment:	
Antipsychotics	166 (98.2)
Mood stabilizers	142 (84)
Benzodiazepines	107 (63.3)
Antidepressants	10 (5.9)

($r=0.21$; $p=0.01$); years of illness ($r=0.22$; $p=0.006$); total number of previous episodes ($r=0.19$; $p=0.02$); number of previous depressive episodes ($r=0.24$; $p=0.005$) and number of days of hospitalization between baseline and 1-month follow-up ($r=0.26$; $p=0.004$).

No significant associations were found between the final FAST total score and the following qualitative variables at baseline (Mann–Whitney U tests): psychiatric comorbidity ($p=0.26$), presence of mixed symptomatology ($p=0.15$); family history of affective disorders ($p=0.61$); history of previous suicide attempt ($p=0.42$) and cannabis consumption at baseline ($p=0.31$). Only the presence of psychotic symptoms during the index manic episode showed a trend to statistical significance ($p=0.059$).

3.3. The prospective model

In order to control for all the variables identified in the Pearson bivariate correlations and Mann–Whitney tests, a multivariate analysis was performed to identify the variables that best predicted functional outcome at 6-month follow-up after a manic episode in the whole sample ($n=169$).

As shown in Table 2, the best model predicting the FAST total score at follow-up included five variables (Adjusted R Square$=0.22$; df$=6$; $F=3.95$; $p=0.002$), explaining between 22% and 29% of the total variance. However, only three out of these six variables were statistical significant, namely: number of previous depressive episodes (Beta$=3.25$; $t=3.23$; $p=0.002$), presence of psychotic symptoms during the index manic episode (Beta$=7.007$; $t=2.2$; $p=0.031$) and Body Mass Index (BMI) (Beta$=0.62$; $t=2.09$; $p=0.041$). Of note, the presence of psychotic symptoms increased the FAST total score at 6-month follow-up in 7 points, and that for every previous depressive episode, the FAST score at follow-up increased 3 points. Even though BMI was statistical significant, the contribution to the FAST total score follow-up was modest; for every additional increase in the BMI, the FAST score increased only 0.6 points.

The remaining variables identified in the model were not statistically significant: number of days hospitalized between visit 1 and 2 (Beta$=-0.133$; $t=-0.75$; $p=0.45$); years of illness (Beta$=-0.16$; $t=-0.92$; $p=0.35$) and hours of sleep at baseline (Beta$=-1.12$; $t=-1.31$; $p=0.194$).

4. Discussion

This study shows that the burden of disease, mainly represented by the number of previous depressions, together with the severity of the present episode (inferred from the presence of psychotic symptoms) and a higher BMI at baseline would play a determinant role in the short-term (6 months) functional outcome following an index episode of acute mania.

The number of previous depressions has already been associated to poor outcome in prior studies (Furukawa et al., 2000; MacQueen et al., 2000). In fact, in MacQueen's et al. (2000) study, it was proposed that the number of past depressions was a stronger determinant of functional outcome than past manias. Moreover, according to their data, the relation between number of previous total episodes (manias and depressions) and functioning was not linear, instead, the greatest drop in functioning occurred relatively early in the course of illness, with a flattening of the curves after five–six total episodes, which will be in accordance with our data, since the mean of total previous episodes in our sample was a total of seven previous episodes. Even though our results are in line with MacQueen and colleagues' data, some authors have found that the relationship between these two variables is the other way around: it is functional impairment and lack of social support that predicts depressive symptoms at follow-up (Weinstock and Miller, 2008, 2010). Though a matter of debate, causality is most probably bidirectional and multifactorial, with one influencing negatively the other.

Psychotic symptoms are thought to be specifier of severity in mental illness (van Rossum et al., 2008). Previous research has reported that the presence of psychotic symptoms is related to poor neurocognitive performance (Martinez-Aran et al., 2008; Thaler et al., 2013). In addition, Levy et al., 2013 found that those patients with psychotic symptoms in their last episode experienced lower psychosocial functioning compared to remitted patients without psychotic symptoms.

On the other hand, a one-year follow-up study found that the clinical variables that best predicted functioning or disability changes over time were Positive PANSS score and mania symptoms, respectively (Tabarés-Seisdedos et al., 2008). The present results, together with the previous literature, point out that the detrimental effects of psychotic symptoms goe beyond the current manic episode and could interfere in the short-term functional outcome.

BMI has also been related to the prognosis and outcome of the illness (Calkin et al., 2009). Weight gain has been reported as a risk factor for poor 12-month functioning after a first manic episode (Bond et al., 2010). In our model, the impact of the BMI at the entry of the study had a relatively small impact on functioning (an increase of 0.6 points in the FAST at the end of follow-up for every increase in the BMI at baseline). Nevertheless, this is a target to be considered for when designing interventions to reduce patients' disability. In fact, a recent study (Sylvia et al., 2013) has proven the efficacy of a new program, named NEW Tx, that focuses on promoting exercise and healthier life-style choices. They found that after that intervention, patients improved their weight, blood/serum cholesterol and triglycerides levels, as well as depressive symptoms and functioning. In addition, there is evidence that bipolar disorder is related to metabolic abnormalities which could reflect a higher “allostatic load” in these patients and thus, a higher burden or more severe form of disease (García-Rizo et al., 2014; Vieta et al., 2013).

Most of the studies assessing the impact of an acute episode on functional outcome have examined first-manic episode patients in relatively young samples (Bond et al., 2010; Conus et al., 2006; Jaeger

Table 2
Regression coefficients predicting FAST total score at 6-month follow-up.

	Beta	t	P
Number of previous depressive episodes	3.25	3.23	0.002
Psychotic symptoms in the present episode	7.07	2.21	0.031
Years of illness (chronicity)	−0.1	−0.92	0.358
BMI at baseline	0.62	2.09	0.041
Number of days of hospitalization (between visit 1 and 2)	−0.13	−0.75	0.454
Hours of sleep	−1.12	−1.31	0.194
Constant	5.73	0.69	0.488

et al., 2007; Kauer-Sant'Anna et al., 2009; Singh et al., 2000; Smith et al., 2014; Tohen et al., 2000, 2011). However, our sample included mainly patients who had presented multiple episodes (mean=7) and whose mean age was higher (mean=42) than those in first manic-episode samples. May be, as a consequence of this, the rate of functionally recovered patients at the end of follow-up in our study was lower (18%) than in other studies (Kauer-Sant'Anna et al., 2009; Tohen et al., 2000) who found rates of 30% and 50% of functionally recovered patients. Despite the rate differences across studies in functionally recovered patients, the reduction in the FAST total score was comparable to another study from a different cohorts that evaluated subsyndromic and syndromic patients (Rosa et al., 2011). Rosa et al., reported a reduction of 9 points at 6-month follow-up while in the present study the reduction in the scale was around 13 points. Of note is that patients without functional recovery (FAST $\geq$ 12) were older, presented more number of previous episodes and more years of illness duration (chronicity). Even though comparing patients with and without functional recovery was not the scope of this study, further research should focus on this issue in order to better understand the causes and consequences and factors involved in functional recovery after a manic episode.

Unlike other studies (Boylan et al., 2004; Correll et al., 2008; Goetz et al., 2007; González-Isasi et al., 2012; Reed et al., 2010; Weinstock and Miller, 2008, 2010) variables of age, gender, low educational level, low level of self-esteem, subsyndromal depressive symptoms and anxiety were not significant in the prognosis of multi-episode patients. These differences may be explained by the variability: in some of them the follow-up period was not performed after an index manic episode (Boylan et al., 2004; González-Isasi et al., 2012; Weinstock and Miller, 2008) or included mixed samples with non-affective psychoses (Correll et al., 2008). In addition, follow-up time varied widely across studies, ranging from four months to three years.

4.1. Limitations

This study has several limitations. The primary one is that the number of previous episodes was determined retrospectively. Even though the collection was performed on the basis of standardized clinical records, the bias of retrospective reporting cannot be ruled out. Another limitation is the lack of assessment of neurocognitive variables at baseline, since its impact on short and long-term functional outcome has been repeatedly demonstrated (Bonnín et al., 2010, 2014). The follow-up period is also questionable as six-month follow-up may be too short to establish predictors of functioning, especially when dealing with chronic samples, which is the case of this study. Finally, other confounding variables that could interfere in the functional outcome, such as family support/functioning, financial resources or pharmacological treatment at baseline were not controlled for.

4.2. Conclusions

Despite the above-mentioned limitations, this study shows that bipolar patients with multiple previous depressive episodes, who suffer from a manic episode with psychotic symptoms, and have greater BMI, are more likely to present functional impairment at 6-month follow-up.

These variables should be taken into account when making estimations of prognosis and weighing benefits and risks of treatments for mania. Although many treatments of acute mania may look similarly effective (Yildiz et al., 2011, 2014), their polarity index may be substantially different (Popovic et al., 2012, 2014), meaning that their ability to prevent further depressive episodes may vary quite substantially. The effective prevention of depressive episodes may be crucial to prevent further disability. Moreover, early treatment of psychotic symptoms may be of importance to avoid the progression and further worsening of the manic episode. Finally, educating patients in healthy lifestyle, including exercise and eating habits, may also help to avoid long-term treatment side effects of those drugs often associated with weight increase or other comorbidities associated to weight gain.

Role of funding

This study has been partially funded by Lundbeck (12/542 & 12/543).

Conflict of interest

Professor Eduard Vieta has served as consultant, advisor or speaker for the following companies: Alexza, Almirall, AstraZeneca, Bial, Bristol-Myers Squibb, Elan, Eli Lilly, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck and Co. Inc., Novartis, Organon, Otsuka, Pfizer Inc, Roche, Sanofi-Aventis, Servier, Schering-Plough, Shire, Sunovion, Takeda, United Biosource Corporation, and Wyeth.

Dr. Gustavo-Vázquez has served as a consultant or speaker for AstraZeneca, Ferrer, Gador, GlaxoSmithKline, Ivax/Teva, Eli Lilly, Lundbeck, Pfizer, Servier and Novartis Pharmaceuticals.

The remaining co-authors have no conflict of interest.

Acknowledgments

The Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III, CIBERSAM, the Spanish Ministry of Education and an unrestricted grant from Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya (2014 SGR 398 to the Bipolar Disorders Group) Beatriu de Pinós, Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement, de la Generalitat de Catalunya i del programa COFUND de les Accions Marie Curie del 7è Programa marc de recerca i desenvolupament tecnològic de la Unió Europea are highly acknowledged.

References

Bond, D.J., Kunz, M., Torres, I.J., Lam, R.W., Yatham, L.N., 2010. The association of weight gain with mood symptoms and functional outcomes following a first manic episode: prospective 12-month data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM). Bipolar. Disord. 12, 616–626.

Bonnín, C.M., Martínez-Arán, A., Torrent, C., Pacchiarotti, I., Rosa, A.R., Franco, C., Murru, A., Sanchez-Moreno, J., Vieta, E., 2010. Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. J. Affect. Disord. 121, 156–160.

Bonnín, C.M., González-Pinto, A., Solé, B., Reinares, M., González-Ortega, I., Alberich, S., Crespo, J.M., Salamero, M., Vieta, E., Martinez-Arán, A., Torrent, C., 2014. Verbal memory as a mediator in the relationship between subthreshold depressive symptoms and functional outcome in bipolar disorder. J. Affect. Disord. 160, 50–54.

Boylan, K.R., Bieling, P.J., Marriott, M., Begin, H., Young, L.T., MacQueen, G.M., 2004. Impact of comorbid anxiety disorders on outcome in a cohort of patients with bipolar disorder. J. Clin. Psychiatry 65, 1106–1113.

Calkin, C., van de Velde, C., Ruzickova, M., Slaney, C., Garnham, J., Hajek, T., O'Donovan, C., Alda, M., 2009. Can body mass index help predict outcome in patients with bipolar disorder? Bipolar Disord. 11, 650–656.

Catalá-López, F., Gènova-Maleras, R., Vieta, E., Tabarés-Seisdedos, R., 2013. The increasing burden of mental and neurological disorders. Eur. Neuropsychopharmacol. 23, 1337–1339.

Colom, F., Vieta, E., Martínez-Arán, A., García-García, M., Reinares, M., Torrent, C., Goikolea, J.M., Banus, S., Salamero, M., 2002. [Spanish version of a scale for the assessment of mania: validity and reliability of the Young Mania Rating Scale]. Med. Clin. 119, 366–371.

Conus, P., Cotton, S., bdel-Baki, A., Lambert, M., Berk, M., McGorry, P.D., 2006. Symptomatic and functional outcome 12 months after a first episode of

psychotic mania: barriers to recovery in a catchment area sample. Bipolar Disord. 8, 221–231.
Correll, C.U., Smith, C.W., Auther, A.M., McLaughlin, D., Shah, M., Foley, C., Olsen, R., Lencz, T., Kane, J.M., Cornblatt, B.A., 2008. Predictors of remission, schizophrenia, and bipolar disorder in adolescents with brief psychotic disorder or psychotic disorder not otherwise specified considered at very high risk for schizophrenia. J. Child Adolesc. Psychopharmacol. 18, 475490.
Furukawa, T.A., Konno, W., Morinobu, S., Harai, H., Kitamura, T., Takahashi, K., 2000. Course and outcome of depressive episodes: comparison between bipolar, unipolar and subthreshold depression. Psychiatry Res. 96, 211–220.
García-Rizo, C., Kirkpatrick, B., Fernández-Egea, E., Oliveira, C., Meseguer, A., Grande, I., Undurraga, J., Vieta, E., Bernardo, M., 2014. "Is bipolar disorder an endocrine condition?" Glucose abnormalities in bipolar disorder. Acta Psychiatr. Scand. 129, 73–74.
Goetz, I., Tohen, M., Reed, C., Lorenzo, M., Vieta, E., 2007. Functional impairment in patients with mania: baseline results of the EMBLEM study. Bipolar Disord. 9, 45–52.
Goldstein, T.R., Birmaher, B., Axelson, D., Goldstein, B.I., Gill, M.K., EspositoSmythers, C., Ryan, N.D., Strober, M.A., Hunt, J., Keller, M., 2009. Psychosocial functioning among bipolar youth. J. Affect. Disord. 114, 174–183.
González-Isasi, A., Echeburua, E., Liminana, J.M., González-Pinto, A., 2012. Predictors of good outcome in patients with refractory bipolar disorder after a drug or a drug and cognitive-behavioral treatment. Compr. Psychiatry 53, 224229.
Grande, I., Hidalgo-Mazzei, D., Nieto, E., Mur, M., Sáez, C., Forcada, I., Vieta, E., 2015. Asenapine prescribing patterns in the treatment of manic in- and outpatients: results from the MANACOR study. Eur. Psychiatry S0924-9338 (15), http://dx.doi.org/10.1016/j.eurpsy.2015.01.003 00047-4.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Hidalgo-Mazzei, D., Undurraga, J., Reinares, M., Bonnín, C.D., Sáez, C., Mur, M., Nieto, E., Vieta, E., 2015. Rev. Psiquiatr. Salud Ment. 8, 55–64.
Huxley, N., Baldessarini, R.J., 2007. Disability and its treatment in bipolar disorder patients. Bipolar Disord. 9, 183–196.
Jaeger, J., Berns, S., Loftus, S., Gonzalez, C., Czobor, P., 2007. Neurocognitive test performance predicts functional recovery from acute exacerbation leading to hospitalization in bipolar disorder. Bipolar Disord. 9, 93–102.
Judd, L.L., Akiskal, H.S., Schettler, P.J., Endicott, J., Leon, A.C., Solomon, D.A., Coryell, W., Maser, J.D., Keller, M.B., 2005. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. Arch. Gen. Psychiatry 62, 1322–1330.
Kauer-Sant'Anna, M., Bond, D.J., Lam, R.W., Yatham, L.N., 2009. Functional outcomes in first-episode patients with bipolar disorder: a prospective study from the systematic treatment optimization program for early mania project. Compr. Psychiatry 50, 1–8.
Levy, B., Medina, A.M., Weiss, R.D., 2013. Cognitive and psychosocial functioning in bipolar disorder with and without psychosis during early remission from an acute mood episode: a comparative longitudinal study. Compr. Psychiatry 54, 618–626.
MacQueen, G.M., Young, L.T., Robb, J.C., Marriott, M., Cooke, R.G., Joffe, R.T., 2000. Effect of number of episodes on wellbeing and functioning of patients with bipolar disorder. Acta Psychiatr. Scand. 101, 374–381.
Martinez-Aran, A., Torrent, C., Tabares-Seisdedos, R., Salamero, M., Daban, C., Balanza-Martinez, V., Sanchez-Moreno, J., Manuel, G.J., Benabarre, A., Colom, F., Vieta, E., 2008. Neurocognitive impairment in bipolar patients with and without history of psychosis. J. Clin. Psychiatry 69, 233–239.
Merikangas, K.R., Jin, R., He, J.P., Kessler, R.C., Lee, S., Sampson, N.A., Viana, M.C., Andrade, L.H., Hu, C., Karam, E.G., Ladea, M., Medina-Mora, M.E., Ono, Y., Posada-Villa, J., Sagar, R., Wells, J.E., Zarkov, Z., 2011. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch. Gen. Psychiatry 68, 241–251.
Popovic, D., Reinares, M., Goikolea, J.M., Bonnin, C.M., Gonzalez-Pinto, A., Vieta, E., 2012. Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder. Eur. Neuropsychopharmacol. 22, 339–346.
Popovic, D., Torrent, C., Goikolea, J.M., Cruz, N., Sanchez-Moreno, J., GonzalezPinto, A., Vieta, E., 2014. Clinical implications of predominant polarity and the polarity index in bipolar disorder: a naturalistic study. Acta Psychiatr. Scand. 129, 366–374.
Ramos-Brieva, J.A., Cordero, V.A., 1986. [Validation of the Castillian version of the Hamilton Rating Scale for Depression]. Actas Luso. Esp. Neurol. Psiquiatr. Cienc. Afines 14, 324–334.
Reed, C., Goetz, I., Vieta, E., Bassi, M., Haro, J.M., 2010. Work impairment in bipolar disorder patients–results from a two-year observational study (EMBLEM). Eur. Psychiatry 25, 338–344.
Reinares, M., Del_Mar_Bonnín, C., Hidalgo-Mazzei, D., Undurraga, J., Mur, M., Nieto, E., Sáez, C., Vieta, E., 2015. Making sense of DSM-5 mania with depressive features. Aust N Z J Psychiatry, pii: 0004867415585583.
Rosa, A.R., Franco, C., Martínez-Arán, A., Sánchez-Moreno, J., Reinares, M., Salamero, M., Arango, C., Ayuso-Mateos, J.L., Kapczinski, F., Vieta, E., 2008. Functional impairment in patients with remitted bipolar disorder. Psychother. Psychosom. 77, 390–392.
Rosa, A.R., Gonzalez-Ortega, I., Gonzalez-Pinto, A., Echeburua, E., Comes, M., Martinez-Aran, A., Ugarte, A., Fernandez, M., Vieta, E., 2012. One-year psychosocial functioning in patients in the early vs. late stage of bipolar disorder. Acta Psychiatr. Scand. 125, 335–341.
Rosa, A.R., Reinares, M., Amann, B., Popovic, D., Franco, C., Comes, M., Torrent, C., Bonnin, C.M., Sole, B., Valenti, M., Salamero, M., Kapczinski, F., Vieta, E., 2011. Six-month functional outcome of a bipolar disorder cohort in the context of a specialized-care program. Bipolar Disord. 13, 679686.
Rosa, A.R., Reinares, M., Franco, C., Comes, M., Torrent, C., Sanchez-Moreno, J., Martinez-Aran, A., Salamero, M., Kapczinski, F., Vieta, E., 2009. Clinical predictors of functional outcome of bipolar patients in remission. Bipolar Disord. 11, 401–409.
Rosa, A.R., Reinares, M., Michalak, E.E., Bonnin, C.M., Sole, B., Franco, C., Comes, M., Torrent, C., Kapczinski, F., Vieta, E., 2010. Functional impairment and disability across mood states in bipolar disorder. Value Health 13, 984–988.
Rosa, A.R., Sanchez-Moreno, J., Martinez-Aran, A., Salamero, M., Torrent, C., Reinares, M., Comes, M., Colom, F., Van, R.W., yuso-Mateos, J.L., Kapczinski, F., Vieta, E., 2007. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin Pract. Epidemol. Ment. Health 3, 5.
Sanchez-Moreno, J., Martinez-Aran, A., Tabares-Seisdedos, R., Torrent, C., Vieta, E., yuso-Mateos, J.L., 2009. Functioning and disability in bipolar disorder: an extensive review. Psychother. Psychosom. 78, 285–297.
Singh, S.P., Croudace, T., Amin, S., Kwiecinski, R., Medley, I., Jones, P.B., Harrison, G., 2000. Three-year outcome of first-episode psychoses in an established community psychiatric service. Br. J. Psychiatry 176, 210–216.
Smith, L.T., Shelton, C.L., Berk, M., Hasty, M.K., Cotton, S.M., Henry, L., Daglas, R., Gentle, E., McGorry, P.D., Macneil, C.A., Conus, P., 2014. The impact of insight in a first-episode mania with psychosis population on outcome at 18 months. J. Affect. Disord. 167, 74–79.
Spearing, M.K., Post, R.M., Leverich, G.S., Brandt, D., Nolen, W., 1997. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI–BP. Psychiatry Res. 73, 159–171.
Sylvia, L.G., Salcedo, S., Bernstein, E.E., Baek, J.H., Nierenberg, A.A., Deckersbach, T., 2013. Nutrition, exercise, and wellness treatment in bipolar disorder: proof of concept for a consolidated intervention. Int. J. Bipolar Disord. 1, 24.
Tabarés-Seisdedos, R., Balanzá-Martínez, V., Sánchez-Moreno, J., Martinez-Aran, A., Salazar-Fraile, J., Selva-Vera, G., Rubio, C., Mata, I., Gómez-Beneyto, M., Vieta, E., 2008. Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. J. Affect. Disord. 109, 286–299.
Thaler, N.S., Allen, D.N., Sutton, G.P., Vertinski, M., Ringdahl, E.N., 2013. Differential impairment of social cognition factors in bipolar disorder with and without psychotic features and schizophrenia. J. Psychiatr. Res. 47, 2004–2010.
Tohen, M., Hennen, J., Zarate Jr., C.M., Baldessarini, R.J., Strakowski, S.M., Stoll, A.L., Faedda, G.L., Suppes, T., Gebre-Medhin, P., Cohen, B.M., 2000. Two-year syndromal and functional recovery in 219 cases of firstepisode major affective disorder with psychotic features. Am. J. Psychiatry 157, 220–228.
Torres, I.J., DeFreitas, C.M., DeFreitas, V.G., Bond, D.J., Kunz, M., Honer, W.G., Lam, R.W., Yatham, L.N., 2011. Relationship between cognitive functioning and 6-month clinical and functional outcome in patients with first manic episode bipolar I disorder. Psychol. Med. 41, 971–982.
van Rossum., I, Haro, J.M., Tenback, D., Boomsma, M., Goetz, I., Vieta, E., van Os, J., 2008. Stability and treatment outcome of distinct classes of mania. Eur. Psychiatry 23, 360–367.
Vieta, E., 2013. Pros and cons of specialised care in bipolar disorder: an international perspective. Br. J. Psychiatry 202, 170–171.
Vieta, E., 2014. The bipolar maze: a roadmap through translational psychopathology. Acta Psychiatr. Scand. 129, 323–332.
Vieta, E., Popovic, D., Rosa, A.R., Sole, B., Grande, I., Frey, B.N., Martinez-Aran, A., Sanchez-Moreno, J., Balanza-Martinez, V., Tabares-Seisdedos, R., Kapczinski, F., 2013. The clinical implications of cognitive impairment and allostatic load in bipolar disorder. Eur. Psychiatry 28, 21–29.
Vieta, P.E., Torrent, F.C., Martinez-Aran, A., Colom, V.F., Reinares, G.M., Benabarre, H.A., Comes, F.M., Goikolea Alberdi, J.M., 2002. [A userfriendly scale for the short and long term outcome of bipolar disorder: the CGIBP-M]. Actas Esp. Psiquiatr. 30, 301–304.
Weinstock, L.M., Miller, I.W., 2008. Functional impairment as a predictor of short-term symptom course in bipolar I disorder. Bipolar Disord. 10, 437–442.
Weinstock, L.M., Miller, I.W., 2010. Psychosocial predictors of mood symptoms 1 year after acute phase treatment of bipolar I disorder. Compr. Psychiatry 51, 497–503.
Yildiz, A., Nikodem, M., Vieta, E., Correll, C.U., Baldessarini, R.J., 2014. A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. Psychol. Med. 1-19.
Yildiz, A., Vieta, E., Leucht, S., Baldessarini, R.J., 2011. Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. Neuropsychopharmacology 36, 375–389.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435.